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DISSERTATION

Submitted to the Board of University Studies of the Johns Hopkins University
in Conformity with the Requirements for the Degree of
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A REVIEW OF THE LITERATURE ON VENOUS BLOOD PRESSURE

Regulation of venous pressure by: 1. Peripheral resistance. It is usually stated that, in general, increased peripheral resistance (in the arterioles)—other things being equal—causes a rise in arterial pressure and a fall in venous pressure and that decreased resistance has the opposite effect.

Bayliss and Starling (7) and Plumier (61) advance the idea that an increased peripheral resistance caused by vasoconstriction decreases the capacity of the vascular system and tends to cause a rise of pressure in all parts of the system. What change will occur in the venous pressure will depend upon whether the influence of the decreased flow from arteries to veins causing a fall, or the decreased capacity of the system causing a rise, predominates. The opposite state of affairs holds in case of decreased peripheral resistance. Sometimes the tendency for the venous pressure to rise is exactly counter-balanced by the tendency to fall. Bayliss and Starling (7) cite, as an illustration, the absence of venous pressure change when vasomotor paralysis has been induced by section of the cord just above the first thoracic segment. Plumier (61) also illustrates this point. He finds no change in venous pressure after weak or strong stimulation of the central stump of the vagus, both vagi being sectioned. In the case of weak stimulation, vasodilatation was produced while strong stimulation produced vasoconstriction. In each case, however, the influence of the peripheral resistance on the venous pressure was balanced by the opposite influence of the change in the capacity of the system.

According to Bayliss and Starling (7), sometimes the venous pressure-raising factor in vasoconstriction of the arterioles predominates, as when the splanchnics are directly stimulated or the vasomotor center

is stimulated by asphyxia. The objections, as advanced by Hill and Barnard (37) and Plumier (61), to attributing this rise in venous pressure to decreased capacity of the vascular system will be discussed later.

2. *Heart rate.* The authors mentioned above (Bayliss and Starling, and Plumier) state that a rise in venous pressure is obtained when the heart slows or stops beating because there is a tendency toward equalization of pressure throughout the system, resulting in a fall in arterial and a rise in venous pressure due to the elasticity of the arteries forcing more blood into the veins. Usually in a slowly beating heart the output per minute decreases and hence the heart does not pump into the aorta per unit of time as much as it did before, thus causing a back pressure in the pulmonary veins, which eventually affects the right heart and causes a rise in the vena cava pressure. This would be true especially when there was an increased resistance to the blood-flow in the arteries, as in vasoconstriction.

Bayliss and Starling (7) consider that most of the rise of venous pressure after peripheral stimulation of the vagus is due to the decreased capacity of the system which comes as a result of the anemic stimulation of the vasomotor center following the low arterial pressure brought about by such stimulation. Their proof of this is that only a slight rise is occasioned by stimulation of the vagus when either the cord or the splanchnics are cut. Plumier (61) has a different explanation for this. He considers the slowing of the heart of primary importance and the vasoconstriction of secondary. He says that cutting the cord or splanchnics causes such a marked vasodilatation (arterial pressure in one of Bayliss and Starling's experiments fell from 120 mm. to 60 mm. Hg.) that tendency toward equalization of pressures cannot show the effect that it would, if the conditions of the vascular system were normal. This point is perhaps brought out more clearly by considering what changes take place in the vascular system under asphyxia, produced by removal of artificial respiration in an animal whose chest has been opened. Bayliss and Starling offer an explanation for this rise in venous pressure, similar to that given in connection with vagus stimulation. Plumier (61) attempts to prove his point that vasoconstriction is of only secondary importance, by comparing the effect of asphyxia before and after section of the vagi. With vagi intact the arterial pressure rises only slightly but the heart beat soon becomes very slow, and coincident with this slowing the venous pressure in the inferior vena cava and the external jugular rises

markedly. As soon as artificial respiration is renewed and the heart beats faster, the venous pressure falls. In the experiment when both vagi are cut, the arterial pressure rises, due to vasoconstriction, but the venous pressure remains unchanged, until (100 seconds after the beginning of asphyxia) the heart becomes paralyzed and consequently slows, and the blood pressure falls. At this time the venous pressure rises. Furthermore, after artificial respiration has been renewed, the arterial pressure rises, due to continued vasoconstriction, and when it is at its maximum the venous pressure has already fallen to normal.

The difficulty here, it seems to me, is in trying to make either heart-slowness or vasoconstriction alone account for the rise in venous pressure. Bayliss and Starling (7) themselves, when discussing the rise of venous pressure after splanchnic stimulation, say (p. 172): "In experiment 5 one of the vagi was intact and the heart was slowed as usually occurs when the splanchnics are stimulated. One might be inclined to ascribe the rise of venous pressure to this slowing of the heart, were it not that in other experiments where both vagi were divided, we still obtained a slight rise on stimulation of the splanchnics." Evidently, then, the slowing of the heart is responsible for the greater part of the venous pressure rise, if not absolutely all. On the other hand, one cannot see how Plumier can be sure that Bayliss and Starling are wrong in ascribing some of their rise in venous pressure, after asphyxia for instance, to the decreased capacity of the system, since no experiment has been performed in which that factor has been ruled out, granting that Bayliss and Starling's attempt to rule it out, not only ruled it out, but introduced a new factor, that of vasodilatation after section of the cord or splanchnics, which vitiated the comparison. It would seem as though this point might be settled by an arrangement, such as that used by Heard and Brooks (31), for keeping the arterial pressure constant under varying experimental conditions. When, after adrenalin or asphyxia with vagi intact, the change in capacity of the system, due to vasoconstriction, was not allowed to be effective, one could then see how much this factor has to do with the rise in venous pressure on slowing of the heart.

3. "*Respiratory pump*." According to Hill and Barnard (37) none of the above explanations is adequate in accounting for the rise of venous pressure obtained as a result of various experimental procedures. They attribute the rise which occurs on arrest of the heart under peripheral vagal stimulation to the respiratory spasms produced, and on asphyxia to strong abdominal and general muscular move-

ments, for in curarized animals these rises do not occur, at least in the case of asphyxia. Their curarization was sufficient to abolish natural respiration, but did not interfere with the heart or tone of the arterial system. As regards vagal stimulation, they say (p. 348), "we ourselves unfortunately have not been able to maintain arrest of the heart in the curarized animal for long enough time to settle this point." Yet in figure 12, page 342 of this article, they show a rise in venous pressure in the same animal on stimulation of the vagus before and after the administration of chloroform. "In the first instance the escape of the heart is complete, the respirations are greatly intensified and by the powerful expiratory spasms of the abdominal muscles the venous pressure is greatly raised. In the second case the inhibition is complete while the respirations, weakened by the chloroform, remain unaltered during the standstill of the heart." On examination of the second curve one sees the venous pressure beginning to rise as soon as the beat of the heart is stopped, but while it is rising the animal was changed to the feet-up position. The venous pressure continues to rise until the heart once more begins to beat. This rise of venous pressure evidently cannot be ascribed to the activity of the respiratory muscles since no change in respiration occurs during the standstill of the heart, nor, probably, to the feet-up position which was assumed during the rise of venous pressure.

These authors object to any explanation of these phenomena which assumes that a rise in venous pressure can be brought about by sending more blood into the venous system, as occurs on arrest of the heart, or by decreasing the capacity of the vascular system by arterial vasoconstriction. They believe that the vascular system is not filled to distention and that since the veins can hold all the blood of the body without distention, no increase in amount of blood in the veins or decrease in arterial caliber can cause a rise in venous pressure. To prove that the veins can hold all the blood of the body at zero pressure they cite the condition that exists in the animal after death. Then, since it might be thought that after death the tone of the vascular system had passed off, they attempt to prove their point in a living animal. After stopping the heart by vagus stimulation, they alternately placed the dog in the vertical feet-down and horizontal positions until all the blood had passed from the arteries into the veins, and past the venous valves so that no reversal of flow could take place. They say (p. 346), "In this experiment we produced a positive pressure in the veins and no pressure in the arteries. . . . Since the arteries are emptied

of blood the whole system is not filled to distention” Just because the arteries are much more elastic than the veins and can, when the heart stops beating, empty themselves of blood and produce a greater positive pressure than before in the veins, it does not therefore follow, it seems to me, that the vascular system, while the heart was beating, was not filled to distention.

Furthermore, in refutation of Bayliss and Starling's belief that anemia of the brain in vagal arrest causes vasoconstriction, they say (p. 348), “In our experiments when the heart has escaped from arrest, there has not occurred any great rise of arterial pressure which we should expect to indicate vasoconstriction.” Why should one expect any great rise of arterial pressure after the heart has begun to beat again? With the resumption of the heart beat and consequent rise of arterial pressure toward normal, the cause of the vasoconstriction, anemia of the brain, is removed.

“Any appreciable increase of vena cava pressure is due either to the reduction of the capacity of the venous system by the action of the respiratory muscles, or to the failure of the heart in maintaining the systolic output” (p. 350). By this, I presume, is meant the inability of a slowly beating heart to expel per minute as much blood as it receives per minute, thus causing a back pressure in the veins. I fail to see how this could cause a rise in venous pressure if their contention is correct, that the venous system is capable of holding all the blood of the body without distention, especially since it occurs almost immediately on slowing of the heart, before the arteries could have emptied the greater part of their blood into the veins. Of course, it may be contended that the cava is only a part of the venous system and it might become distended when a large amount of blood collected in it, but this hardly seems a valid contention in the case of the immediate rise in venous pressure on arrest of the heart.

4. *Chemical mechanism.* Roy and Brown (64) in experimenting with the frog's web, tongue and mesentery, found that temporary anemia was followed by dilatation of arteries, capillaries and veins. This dilatation they attribute to a “relative diminution in the lymph of certain of the constituents of the blood, or the presence in increased amount of certain of the products of tissue exchange, or both of these combined” (p. 359). This effect, they say, is independent of cerebro-spinal vasomotor effects; it may possibly be due to action on peripheral vasomotor ganglia, but they think it is more probably due to direct action on vessel walls. These causes operate in other congestions and

the authors feel that this automatic regulation of the peripheral circulation is of very great importance.

Henderson and Harvey (33), and Henderson (32) develop the idea of a peripheral chemical control of venous pressure "largely through variations in the CO_2 content of the venous blood." CO_2 , by relaxing the veins, they believe, removes the resistance to the flow of blood from capillaries to veins, and so causes an increase in venous pressure. They speak of such a relaxation as though it were merely the complete or partial removal of a clip, allowing more blood to flow into a vessel whose caliber remains the same. But if relaxation means more than this; if it means an actual increase in the capacity of a portion of a blood vessel, due to the lessening of vascular tone, it is difficult to see how this relaxation can cause a rise in the pressure in the vessel even though there is an increased amount of blood present.

5. *Nervous mechanism.* In a study of the regulation of the blood supply of the brain in 1890, Roy and Sherrington (65) found that stimulation of the peripheral stump of the vago-sympathetic nerves in dogs produced sometimes a rise, sometimes a fall of general venous pressure. They think that this probably means that the vago-sympathetic trunk contains vasomotor fibers to the veins. As discussed in the section on heart rate, later observers have attributed this rise which peripheral vagus stimulation gives, to the slowing of the heart which is occasioned by such stimulation. Slowing of the heart due to paralysis from asphyxia with both vagi cut has been shown by Plumier to give a rise in venous pressure comparable to the rise caused by peripheral vagus stimulation. This perhaps does not prove that the vago-sympathetic nerves possess no venomotor fibers, but there seems to be perfectly adequate explanation for the venous pressure change without assuming the existence of such venomotor fibers. That Roy and Sherrington sometimes found that stimulation of the peripheral stump of the vago-sympathetic nerves produced a fall in general venous pressure, may possibly have been due to an escape of current to the central end of the nerve through the fluid medium surrounding the tissues. One cannot tell what happened to the heart rate in these cases of a fall in venous pressure for no graphs are given or statement made in regard to it.

Thompson (72) in 1893 observed constriction of the superficial veins of the hind limb of dogs and rabbits on stimulation of the sciatic nerve or the spinal cord. The constriction took place in short sections, the diameter of the vein between the segments remaining unchanged. Bancroft (3) confirmed these observations and extended the work.

He observed the appearance of the veins of the hind limb of a cat (rabbits also were used but were not found nearly as satisfactory) before and after section of various nerves, and thus traced out the vasomotor supply. The cell body of the pre-ganglionic fiber lies in the spinal gray matter, the axis-cylinder emerging in the anterior root of the 1st, 2nd, 3rd or 4th lumbar nerve, following the corresponding white ramus into the sympathetic chain, running down it for a certain distance. The cell body of the post-ganglionic fiber lies in the 6th or 7th lumbar sympathetic ganglion, the axis-cylinder running to the veins in the sciatic nerve. Langley's nicotine method was used to determine the position of these ganglia.

The experiments of Gunn and Chavasse (30) and Crawford and Twombly (18) on the effect of epinephrin on isolated veins lend support to the belief that a venopressor nervous mechanism exists in the veins. The details of these experiments will be given later in this paper under the head of adrenalin.

Hooker (41), (42) has demonstrated veno-pressor fibers in a nerve trunk running from the inferior mesenteric ganglion to the veins of the large intestine. A rise in venous pressure in an isolated loop of intestine was induced by stimulation of: *a*, the nerve to the part (peripheral mechanism); *b*, a sensory nerve such as the saphenous (central reflex mechanism); *c*, the central mechanism by asphyxia. Section of the peripheral nerve or destruction of the medulla destroyed the reflex. A probable failure of this mechanism in shock is predicated by Morison and Hooker (55).

A contraction of the veins seems to be the cause of the increased capillary pressure found in the blue-handed type of irritable heart cases as described by Briscoe (9). This is especially illustrated in those patients whose hands were sometimes normal and sometimes blue. The average readings of this class, when the hands were normal, were: venous pressure, 10.6 cm. H₂O; capillary pressure 25.3 cm. H₂O; and when blue were: venous pressure, 10.6 cm. H₂O; capillary pressure, 33.3 cm. H₂O. Whether this contraction of the veins falls under the chemical mechanism theory or the nervous mechanism theory, the author does not state. One presumes, from the article, that it is the latter.

It is not intended in this paper to review in detail the literature on portal venous pressure, as it forms a rather specialized type of venous pressure. A comprehensive review of the literature which has established the presence of a vasomotor mechanism in the radicles of the

portal vein, is to be found in Burton-Opitz's (13) and Edmunds' (22) papers.

Effect on venous pressure of: 1. Adrenalin. a. Effect on isolated veins. Dunn and Chavasse (30) have tested the effect of adrenalin (1 to 100,000) on isolated ring preparations from various veins in the sheep (external jugular, mesenteric, superior and inferior cava) and find a constriction similar to that which occurs in the arteries. The external jugular gave a greater response than the superior and inferior cavae. The amount of response of the mesenteric vein could not be compared with that of the other veins, for the temperature in the case of the mesenteric was 41°C., while in the other experiments it was 36°C. From this they judge that the veins probably contain veno-constrictor nerve fibers from the thoracico-lumbar sympathetic nervous system. Crawford and Twombly (18) corroborate these observations, finding constriction of ring preparations from femoral, iliac and saphenous veins of the dog. Their work on roosters is interesting in that they find some veins that contract in adrenalin solutions, and others that do not. Rings of the jugular vein of white Leghorn roosters, taken from the middle of the neck, contract slowly with 1 to 60,000 adrenalin in oxygenated Ringer's solution, but rings from the jugular vein near the head and from the large vein of the wattles gave no response. This argues, they feel, against a vasomotor supply to the cephalic end of the jugular vein and the veins of the wattles, and they suggest that perhaps the absence of vasoconstrictor fibers in wattles may be one of the reasons why they blue so easily.

b. Effect of intravenous injections. Hill (36) found that intravenous injection of suprarenal extract into a dog whose vagi had been divided caused a rise in arterial pressure of 1170 mm. MgSO_4 solution, while the vena cava pressure remained unaltered. Plumier (61) attributed the rise in superior and inferior vena cava pressure, which he obtained on intravenous injection of adrenalin in the intact animal (dog), to the slowing of the heart which such an injection occasions. He feels that one does not get as great a rise with say a 0.4 mgm. injection as the slowing of the heart would seem to indicate, but this may be explained by the fact that the increased force of the heart beat tends to reduce the venous pressure. However, after cutting the vagi, unless a very large dose is administered, there is no change or only a slight rise in venous pressure. In both cases there was important vasoconstriction resulting in a considerable rise in arterial pressure, but this decreasing of the capacity of the vascular system, he points out, is not sufficient,

in itself, to change the venous pressure. Capps and Matthews (16) find that a small dose (they do not state the amount) of adrenalin does not affect the venous pressure, but a large dose, such as $\frac{1}{8}$ mgm. (2 minims) of 1 to 1000, causes a rise of from 10 to 80 mm., and that coincident with this rise, the heart is markedly slowed. "The rise in venous pressure was coincident with this halting, irregular action of the heart, and it remained high until the normal rhythm returned. We found likewise that, in a slow or inhibited heart-action from exciting the vagus nerve with faradic current, the venous pressure rose. Hence it seems probable, as Plumier (61) states, that the rise in venous pressure after large doses of epinephrin is explained by the halting heart-action rather than by any venomotor stimulation" (p. 390). Bainbridge and Trevan (2) exclude reflex vagus inhibition in their experiments by a small dose of atropin early in each experiment. Under these conditions they find little or no change in vena cava pressure after adrenalin injection into a portal tributary or systemic vein (hepatic artery tied or intact), but a rise in portal pressure due, they think, either to a swelling of the columns of the liver cells narrowing the capillary channels, or constriction of the radicles of the portal vein. Two cubic centimeters of a 1 to 10,000 solution of adrenalin cause a rise in portal pressure equal to 255 mm. of sodium citrate solution. Kuno (50) explains the slight rise in venous pressure which he obtained on injection of adrenalin, with the heart beating faster, by saying, "the contraction of the blood vessels evoked by adrenaline is most distinct in the arterial system so that a large amount of blood might escape into the veins. The pressure in the veins does not therefore fall, on the contrary it rises more or less during action of the adrenaline although the heart works extremely energetically" (p. 232).

As far as I know, no measurements have been made of the effect of adrenalin on venous pressure in man. A word of caution should, therefore, be given about transferring data concerning adrenalin from animals to man. As has been noted above, the rise of venous pressure in dogs has been attributed to the concomitant slowing of the heart. In man, however, adrenalin does not slow, but quickens the heart rate.

Clinical findings reported by Donaldson (21) and Miller (54) indicate that in practically every person (normal or pathological) adrenalin injection causes no change or causes an increase in pulse rate. Only one case of a fall in pulse rate was reported (Donaldson) and this was in a patient much collapsed from hemorrhage. With the subcutaneous

injection of 0.5 cc. of 1 to 1000 adrenalin, used in the "Goetsch" test (29), (57), there is no reaction on the part of normal patients and an increase of ten to fifty beats per minute in patients hypersensitive to adrenalin. This result is further corroborated by the work of Wearn and Sturgis (74) and of Tompkins, Sturgis and Wearn (73). Therefore it would be incorrect to assume that the results obtained by Capps and Matthews (16) on dogs, in their studies on "venous blood-pressure as influenced by the drugs employed in cardiovascular therapy," necessarily apply to man. Similarly, Meek and Eyster's conclusion (53) (based on experiments on unanesthetized dogs with good vagal tone), that adrenalin cannot be the immediate cause of cardiac acceleration which follows moderate exercise, because the heart slows after adrenalin, cannot be held good for man in whom the heart increases its per-minute rate after adrenalin. Still another example of the different way in which adrenalin affects the same structure in different animals is given by Barbour (5), who found that adrenalin caused constriction of human coronary arteries, but relaxation of the coronary arteries of the calf, sheep and pig.

2. *Various other influences.* Since the experimental work in this paper deals only with the effect of adrenalin on venous blood pressure, it does not seem appropriate to review, in detail, the effect of various other influences on venous pressure. The following references may, however, serve to make this general review of the subject more complete. The relation of venous pressure to:

a. *Gravity.* Hill (35); Hill and Barnard (37); Barach and Marks (4)

b. *Respiration.* Jacobson (46); Wertheimer (75); Hill and Barnard (37); Burton-Opitz (12); Plumier (61).

c. *Exercise.* Burton-Opitz (11); Hooker (38); Elpers (23); Jones (47); Henderson and Harvey (33). Krogh's (49) recent work on the effect of exercise in opening up new capillary beds, is of interest in this connection.

d. *High altitudes.* Schneider and co-workers (66), (67), (68), (69); Kellaway's (48) work on the relation of anoxemia to the output of adrenalin may throw some light on the question of the effect of high altitudes on venous pressure.

e. *Increased atmospheric pressure.* Hill (36).

f. *Drugs, other than adrenalin.* Hill and Barnard (37); Plumier (61); Burton-Opitz (14); Capps and Matthews (16).

g. *Injection of physiological solution.* Bainbridge (1); Kuno (50).

Venous pressure work on man. A review of various methods for measuring venous pressure in man is found in an article by Hooker and Eyster (43), in the Johns Hopkins Hospital Bulletin for 1908. The following is a list of articles dealing with these methods:—Oliver, 1898, (58); Frey, 1899, (26); 1902, (27); Gaertner, 1903, (28); von Basch, 1904, (6); Sewall, 1905, (70); von Recklinghausen, 1906, (62); Oliver, 1907, (59); Moritz and von Tabora, 1910, (56); Frank and Reh, 1912, (25); A. A. Howell, 1912, (45); Lombard, 1912 (51); Hooker and Reese, 1914, (44); Hooker, 1914, (39); Brown, 1918, (10); Wiggers, 1918, (76). For comparison with the normal venous pressure values in man, given in the above articles, it may be of interest to note the venous pressure values obtained by Jacobson, 1867, (46), in sheep, and by Burton-Opitz, 1903, (12), in dogs.

Pathological values are given in the articles by Calvert (15); Hooker and Eyster (43); A. A. Howell (45) and Clark (17). Diurnal variations are given by Oliver (60); Hooker (39) and Clark (17); the effect of age and sex on venous pressure by Elpers (23) and Hooker (39), (40), and the effect of temperature by Elpers (23); Hewlett (34) and Hooker (39).

AN EXPERIMENTAL STUDY OF THE EFFECT OF ADRENALIN ON VENOUS BLOOD PRESSURE

Introduction. It is evident from the foregoing discussion that in studying the effect of any drug on venous blood pressure, one must take into consideration the effect of this drug on the various mechanisms, changes in which are known to cause changes in venous pressure. So close is the relationship between the various parts of the circulatory, vasomotor and respiratory systems, that any change in one part usually causes changes in several other parts. Hence, a change in venous pressure must very often be ascribed to the operation of several factors, sometimes supplementing, sometimes antagonizing one another. Sometimes one factor is so predominant than any other is lost sight of. This seems to have been the case in the previous study of the effect of adrenalin on venous pressure. A greatly slowed heart causes a rise in venous pressure. Adrenalin, injected into the blood stream of dogs with good vagal tone, causes slowing of the heart and a rise in venous pressure. Naturally, the conclusion was that the rise in venous pressure was due to the slowing of the heart rate, especially since little change in pressure occurred on administration of adrenalin to these dogs after vagotomy.

It has been demonstrated for sheep by Gunn and Chavasse (30), and for dogs and roosters by Crawford and Twombly (18), that adrenalin chloride causes contraction of isolated vein rings. The work of Bainbridge and Trevan (2) indicates that the radicles of the portal vein in the intact animal contract under the influence of adrenalin. Nerves to the veins of the limb have been demonstrated by Thompson (72) and Bancroft (3), and to the portal vein by Mall (52) and others. The experiments of Hooker (41), (42), demonstrate the existence, in the intestinal veins at least, of a nervous constrictor mechanism, which can be stimulated directly or indirectly. In view of this evidence, one naturally wonders whether or not such a nervous mechanism is functioning when adrenalin chloride is introduced into the circulation, and if the general venous pressure rise occasioned thereby is not, in part at least, due to a constriction of the veins. No evidence, as far as I know, has been found that points to such a mechanism coming into play after adrenalin, except in the case of the portal vein.

It is with these things in mind that the present investigation has been undertaken, to ascertain what factor or factors are responsible for the general rise of venous blood pressure which follows the intravenous injection of a solution of adrenalin chloride.

Experimental procedures. In the course of these experiments about fifty dogs and twenty-five cats were employed, weighing, on the average, 8 kgm. and 2.3 kgm., respectively. The experiments on dogs were carried out under ether anesthesia. The cats were decerebrated according to the method described by Sherrington in his recent laboratory manual (71), an anesthetic, ether, being used only during the procedures prior to the decerebration. The decerebrate cat preparations were always kept on an electric pad throughout the experiment.

Arterial pressure was recorded by a mercury or a Hürthle manometer, sometimes by both. Venous pressure was recorded as follows: brass cannulae (7 cm. long by 1 to 1.5 mm. bore, for cats, and 16 cm. by 2 to 2.5 mm., for dogs), connected with manometers containing 2 per cent sodium citrate, were inserted in the external jugular and femoral veins and pushed in past the valves so that the pressures recorded were those in the superior and inferior cavae. Whenever there was any doubt that the cannulae were not properly inserted, a dissection was made at the end of the experiment. The entrance of the superior cava into the heart was taken as the zero level for pressure. To make sure, from time to time, that no clots had formed, the pressure was raised in the manometer, by means of a pressure bottle, to

several centimeters above the pressure existing in the vein and the citrate solution then allowed to run into the vein. This it did promptly, if there was no obstruction. It was always noted on the tracing when such a procedure occurred. Controls were made which showed that injections of such amounts of 2 per cent sodium citrate ($\frac{1}{2}$ to 1 cc.) had no visible effect on the circulatory system, and the amount of fluid injected was insufficient to cause any change in venous pressure.

Simultaneous tracings of arterial pressure, respiration and time relations were made on a smoked paper kymograph. Since the experimenter worked alone, it was necessary to resort to some method of recording, so that venous pressure readings could be made and injections carried out and recorded by one person, and the exact correspondence between the various pressures be noted on the tracing. One lever recorded respiration, another the arterial blood pressure, and a signal magnet, which marked the base line for the arterial pressure (mercury manometer), recorded the duration of the injection and was also connected with a Harvard clock recording half-minutes. In this circuit there was an electric buzzer which signaled every time the marker was recording a half-minute, and at the sound the level of the venous pressure manometers was noted, the pressures later being marked at the proper place on the tracing. On the same line with this marker, and writing only a millimeter or two behind it, a Jacquet chronograph recorded seconds.

Parke, Davis & Company's adrenalin chloride 1 to 1000 solution was used throughout. Before injection, it was diluted with 0.7 per cent sodium chloride to the desired strength, usually 1 to 10,000.

Special experimental procedures, not followed in all experiments, are described in connection with the experimental data obtained from those procedures.

Of course, if small rises of venous pressure are to be considered significant, one must make sure that they are not caused by the introduction of fluid, used in the injection. For this reason, very small amounts of adrenalin solution were slowly injected (in most cases 0.5 to 3.0 cc. in 5 seconds or more), and control experiments were several times made to ascertain how large an amount of 0.7 per cent NaCl had to be introduced to cause any change in venous pressure. One-half to 3.0 cc. were without effect, 5.0 cc. caused a rise of 3 or 4 mm., while 20.0 cc.—a larger amount than was ever employed in adrenalin chloride injections—caused a rise of only 10 or 15 mm. Na citrate solution.

Experimental work on: 1. Changes in peripheral resistance and capacity of the vascular system. Under all conditions studied, adrenalin always caused a rise in arterial pressure due to arterial constriction. The rise was higher for the same dose when the heart rate was increased than when it was decreased, but there was always a rise. Such a constriction, other things being equal, would tend to cause a fall in venous pressure due to the obstruction to the flow from arteries to veins but, on the other hand, the decreased capacity of the system brought about by arterial constriction would tend to raise the pressure in all parts of the circulatory system. In some cases of arterial constriction, as shown by Bayliss and Starling (7) and discussed in the historical review in this paper, the two factors may balance and give no change in venous pressure. There is one factor here which seems to have received little notice in this connection, and that is the rate at which plasma may leave the blood stream under varying arterial pressures. How far this may operate toward compensating the "decreased capacity of the system" factor, is not known. At all events, in the case of adrenalin, when all other causes for change in venous pressure are ruled out, as far as possible, these factors of peripheral resistance and capacity of the system seem to balance, for no change in venous pressure occurs. Chart 1 (I and II) illustrates this point. About a quarter of an hour after the decerebrated cat (chart 1, I) was curarized, according to the procedure described under "respiration," 0.15 mgm. (3 cc.) of adrenalin chloride was injected into the right femoral vein causing no change in vena cava pressure, although the arterial pressure was raised from 34 to 167 mm. Hg.

Chart 1 (III and IV) shows an experiment in which the venous pressure fell after adrenalin, a very unusual occurrence. It is probable that, in this case, the increased peripheral resistance so obstructed the flow from arteries to veins that there occurred a fall in venous pressure. The decrease in heart rate would tend to cause a rise in venous pressure, but this was apparently overbalanced by the factor or factors tending to cause a fall. In any case, it seems evident that the usual rise in venous pressure caused by adrenalin is not brought about, directly, by changes taking place in the arteries, though, as will be explained later, a rise in arterial pressure may assist in causing a rise of venous pressure when it occurs in conjunction with a slowing of the heart.

2. Chemical regulation. It is conceivable that adrenalin may act as a chemical stimulant to venous musculature, independent of any effect

CHART NO. 1

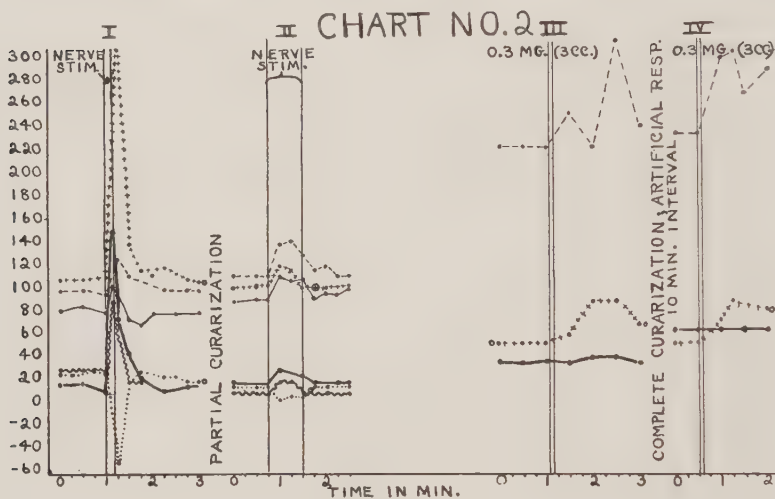
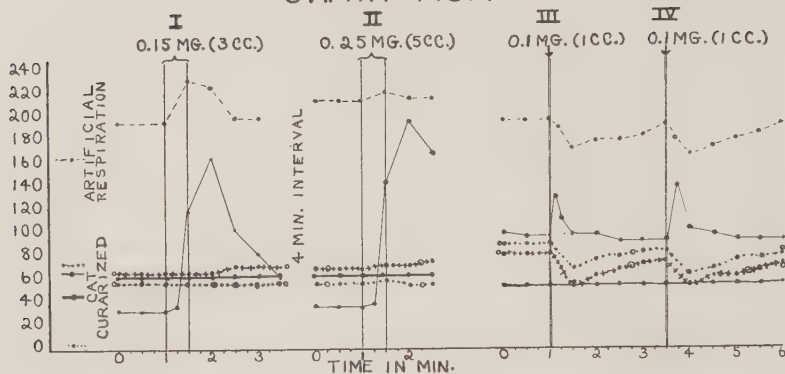
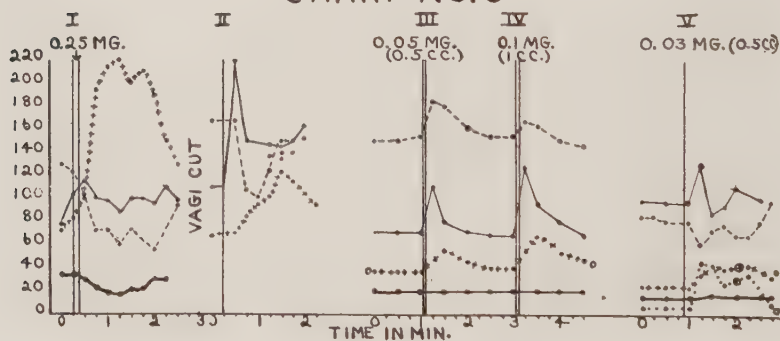


CHART NO. 3



through a nervous mechanism. As far as I know, no work has been done on this subject. However, adrenalin produces an effect upon venous rings similar to that upon arterial rings, and it seems reasonable to assume, until disproved, that in the veins, as has been shown for the arteries, adrenalin acts by stimulating the myoneural junctions of the sympathetic nerve fibers in the vascular musculature.

3. *Respiratory and muscular factors.* The contraction of muscles against the veins, as in exercise, and changes in respiration, are known to be very efficient in causing changes in venous pressure. Take for example chart 2 (II), showing the result of stimulation of the saphenous nerve before and after administration of curare. The dog was not completely curarized, as can be seen from the fact that a slight change in rate and amplitude of respiration was elicited by strong sensory stimulation. The interesting thing is that the venous pressure response seems to bear a definite relation to the amount of respiratory response. When adrenalin chloride is injected in small amounts (usually 0.1 to 0.3 mgm.) there may be no respiratory response, or a decrease in height and frequency of respiration occurs. This change evidently has little or nothing to do with the rise in venous pressure, since that rise takes place when no respiratory variations occur, and a decrease in rate causes a fall, not a rise in venous pressure. However, to fully rule out any change in venous pressure due to muscular contraction or respiratory change, curare was administered in a number of experiments, and as soon as breathing ceased artificial respiration was given. The air was heated to 30°C. before reaching the animal. To be sure that other muscles besides the respiratory muscles were paralyzed, the

----- pulse rate per minute.

———— arterial pressure in mm. Hg.

..... superior cava pressure in mm. 2 per cent sodium citrate.

++++ inferior cava pressure in mm. 2 per cent sodium citrate.

———— respiratory rate per minute.

Wavy line, respiratory amplitude (relative only).

Large dots indicate actual determinations.

Circles indicate that venous pressure cannula was tested and found free of clots.

Chart 1. Adrenalin chloride injections: I and II, decerebrate cat 7; III and IV, dog 4 B.

Chart 2. I and II, dog 35 A—Stimulation of saphenous nerve before and after partial curarization; III and IV, decerebrate cat 9—Adrenalin chloride injections, before and after complete curarization; vagi cut.

Chart 3. Adrenalin chloride injections: I and II, dog 1 A, vagi cut between I and II; III and IV, dog 4 B; V, dog 29 A.

minimal nerve stimulus necessary to cause contraction of some skeletal muscle in the fore limb was determined before curare, and then sufficient curare was given to cause this stimulus and other stronger stimuli to become ineffective. In such experiments adrenalin had practically the same effect on the venous pressure before and after curare: chart 2 (III and IV) is an example. Changes in the rate of the artificial respiration seem, also, to be ineffective. It has been noticed a number of times that the venous pressure response to adrenalin is not as marked immediately after the administration of curare as it is later. In a few cases, as shown in chart 1 (I and II), the effect persists. This depressant action on venous pressure response is probably due to an action on the nervous mechanism in the veins. That it usually passes off very rapidly, fits in with the general idea that the primary depressant action of curare on the circulatory system is of very short duration.

When not curarized, occasionally the act of injecting was a sufficient sensory stimulus to cause a muscular response. This muscular response, often seen in a stretching out of the lower limbs and consequent stretching of the abdominal muscles, was not evident on the tracing given by the usual pneumograph. Therefore, instead of recording respiration by means of a rubber bag around the chest, a small rubber balloon was inserted through a small opening into the abdominal cavity near the diaphragm, and the skin closed tightly around the glass tube to which the balloon was attached. The balloon was then blown up until it held about 5 cc. air, and connected with a recording tambour and lever as the bag around the chest had been before. This has the advantage of recording not only respiratory changes but also changes in abdominal pressure which very markedly influence venous pressure, as shown by Hill and Barnard (37).

4. *Heart rate and output per minute.* Plumier (61), in his work on venous pressure, laid great stress on slowing of the heart rate as a very efficient means of raising the venous pressure. Occasionally the heart suddenly stops beating after an injection of adrenalin. The venous pressure may then rise very high; in one case it rose five times as high as it had after a similar dose of adrenalin when the heart rate was increased. In dogs with good vagal tone, the heart usually slows markedly after adrenalin and the venous pressure rises (see chart 3, I). Even with the vagi cut the pulse rate is often slowed, due probably to a direct action on the heart musculature, as is shown in chart 3 (II). A rather uncertain venous pressure response is often seen in vagotomized dogs when the heart rate is increased after an adrenalin injection.

Such results would lead one to attribute the rise in venous pressure solely to the decreased heart rate as did Plumier (61) and, later, Capps and Matthews (16). Chart 3 (III, IV and V), however, makes one doubt that heart rate is the only factor involved. Work on dogs under ether did not prove satisfactory in clearly demonstrating whether or not a nervous mechanism played some part in venous pressure response to adrenalin. There are several reasons for this. In order to rule out the slowed heart rate, the vagi had to be cut. This caused a very great increase in the depth of respiration which brought about such a marked rise and fall in venous pressure that it was difficult to compare such fluctuations in pressure with the change occurring after adrenalin, since the respiratory variations were then often absent, due to temporary cessation of respiration. Besides, even with the vagi cut, the heart frequently slowed after adrenalin. Still more serious, perhaps, is the possible effect of ether on the nervous mechanism. Ether depresses the arterial vasomotor response to adrenalin, as shown by Berry (8) and Rous and Wilson (63), and could naturally be expected to affect a nervous mechanism in the veins—all the more so because, as shown by Hooker (41), this mechanism is extremely sensitive. If very light ether anesthesia were employed, there would then be the difficulty of muscular and respiratory responses discussed above. Chart 3 (III and IV) shows an unusual experiment in which the ether anesthesia was light, and yet respiration remained constant throughout the experiment. Experiments on decerebrated cats, which needed no anesthetic after the operation, and whose vagal tone is not nearly so marked as dogs', proved to be very satisfactory. Also, it was no small consideration, since curare is very difficult to obtain, that it took only a small amount of curare to curarize a cat, as compared with a dog. Since sensory stimuli have been shown to be effective after curare, it is desirable, for humanitarian reasons, to work on a decerebrated preparation where there can be no question of not giving enough anesthetic during curarization to cause analgesia.

Concerning the influence of change of the heart rate on venous pressure, it should be said that it is really the per-minute output of the heart, rather than the heart rate alone, that is essential. Quoting from Erlanger and Hooker (24), (p. 161), "If the pulse pressure is approximately dependent upon the amount of blood that escapes from the arteries during one cardiac cycle, then it is obvious that the amount that escapes must vary directly as the pulse rate." Therefore, pulse pressure multiplied by pulse rate gives us an expression of the output

of the heart per minute. It is possible to increase or decrease the output per minute by increasing or decreasing either or both of these factors, and to keep the output constant by varying the two factors proportionately in the opposite directions. Hence one cannot say that a slowed heart necessarily causes a decreased output per minute, and hence a rise in venous pressure. It is theoretically possible that the pulse pressure might so increase that even with a lower heart rate the output per minute would increase. In the case of adrenalin, however, this possibility seems never to be realized, at least when the pulse rate is greatly reduced. For example, in one experiment, before adrenalin, the pulse pressure was 180 mm. Hg. and the pulse rate per minute 158, making a per-minute output of 28,440. After adrenalin, the pulse pressure was 240 and the pulse rate 20, giving the greatly decreased per minute output of 4800. The slowing in this case was way out of proportion to the increased pulse pressure, and was accompanied by a rise in venous pressure from 25 to 120 mm. Na citrate.

Experiments were performed on dogs, as illustrated in chart 4, in which the vagi were cooled by perfusing ice water through glass tubing in a V around each nerve, and afterwards allowing the nerves to come to room temperature again. The pulse rate, arterial pressure, respiratory rate and amplitude were all affected but very little change in venous pressure took place. When the perfusion of ice water around the nerves was discontinued, the pulse rate decreased from 144 to 108, the venous pressure decreasing also a few millimeters. When the heart stops beating the rise in venous pressure is due to a back pressure in the veins and also to the tendency for equalization of pressures to take place throughout the vascular system. When the heart slows, but does not stop, these factors operate to cause a rise in venous pressure, but to a less extent. If now the arterial pressure rises as the slowing of the heart occurs, as after adrenalin, the mean pressure of the vascular system toward which the various pressures are tending will, of course, be greater, and hence there is a much greater possibility of a large rise in venous pressure. In one experiment, after an adrenalin injection, the heart was slowed about as much as after the cooling of the vagi was discontinued (chart 4, II). In the former case the arterial pressure rose, showing that the capacity of the vascular system was decreased; while in the latter it fell. In the case of adrenalin there may be a nervous constrictor mechanism in the veins at work, but from other experiments on dogs it seems likely that this plays little part in etherized dogs. It seems more probable that the

decreased capacity of the system acts in connection with the slowed heart rate to cause a rise in venous pressure.

5. *Nervous mechanism.* It can readily be seen from the foregoing that one cannot attribute a rise in venous pressure to the activity of a vasomotor mechanism in the veins, unless one is sure that the per-minute output of the heart has not decreased sufficiently to explain the rise. As we have seen, when this factor is ruled out in experiments on dogs under ether, the evidence for the functioning of a nervous mechanism is not very conclusive. In the experiments on decerebrate cats, however, there is clear evidence of such a mechanism. With the vagi intact, we may get the response which is usual in dogs—a rise in venous and arterial pressure and a slowing of the heart, chart 5 (I and II). When, however, the vagi are cut (chart 5, III and IV), there is still a rise in venous pressure. The heart rate is practically unchanged and the pulse pressure increased (as nearly always occurs after adrenalin) so that the output per minute is now increased and the tendency would be for a fall rather than a rise in venous pressure. So also in this experiment, the respirations were decreased in height and frequency which would tend to lower rather than raise venous pressure. The rise, therefore, which one does get under these circumstances seems to be due to a nervous factor, rendered probably less effective in producing a rise because of the factors tending to produce a fall. Chart 6 shows very uniform rises in venous pressure, though in some cases the heart rate is slowed and in some cases increased in frequency. In the experiment shown in chart 7, the respiratory factor is completely controlled by curarization. The vagi are cut in IV and V.

It is interesting to inquire whether or not the seat of this action of adrenalin is central or peripheral. Two different types of experiments were performed to investigate this question. In the first, the cord was sectioned in the cervical region (about at the level of the fifth or sixth cervical vertebra). As is shown in chart 8, this does not destroy the venopressor response to adrenalin, though whether or not any small part of the reaction is of central origin is hard to determine, since the amount of response to a certain dose is not invariable, and so the effect of a dose before cutting the cord is difficult to compare with the same dose just afterwards. The response before and after is quite similar, however.

For the second type of experiment the isolated vein preparation of Hooker (41) was used. In the first of these experiments, Doctor Hooker kindly demonstrated the method to the writer. An isolated loop

CHART NO.4

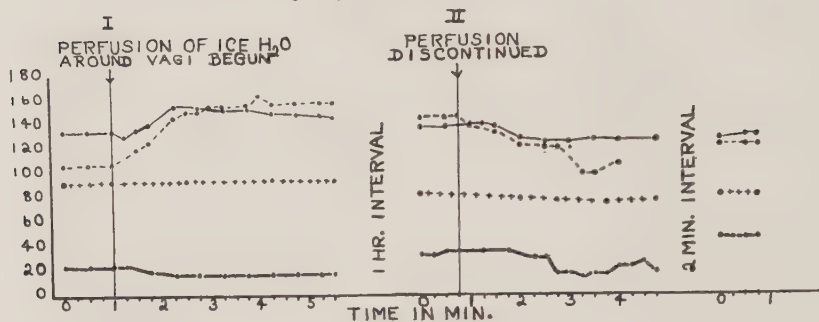


CHART NO.5

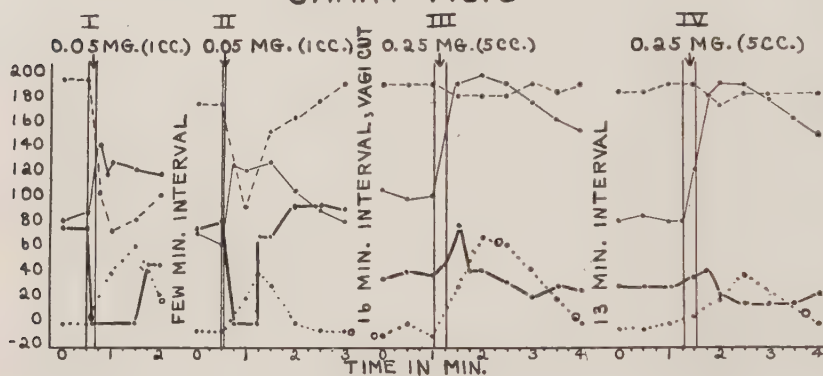
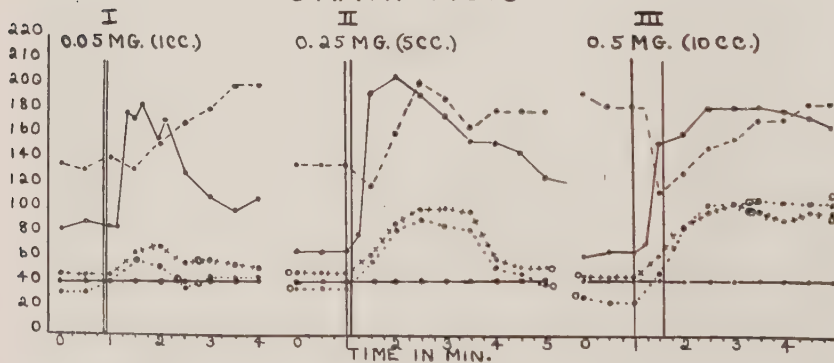


CHART NO.6



of large intestine in which the inferior mesentery artery and vein had been cannulated, was hung up free from the surrounding intestines. The only connection with the animal was through a nerve running from the inferior mesenteric ganglion to the large intestine and entering the intestine in close proximity to the inferior mesenteric artery. Blood was washed out of the vessels from artery to vein by means of warmed (about 37°C.) Ringer's solution under air pressure of 90 to 120 mm. Hg. The cannulated artery was then disconnected from the air pressure apparatus and allowed to hang freely from the preparation. The vein was then connected with a venous pressure manometer containing warmed Ringer's solution. The zero level was, in most cases, adjusted to the level of the vein in which the pressure was being measured. The vein was distended by a positive pressure of from 30 to 100 mm. Ringer's solution, by means of a pressure bottle. Any change in the caliber of the vein would then be indicated by a rise or fall in the level in the venous pressure manometer. Hooker (42) has shown that, in this preparation, a rise in venous pressure may be elicited, peripherally, by stimulation of the nerve to the part; reflexly, by sensory stimulation; and centrally, by asphyxia. In such a dog, when adrenalin chloride was injected into the saphenous vein in doses from 0.2 to 0.6 mgm., no rise in venous pressure in the isolated vein occurred, but when such injections were followed by asphyxia, produced by closing off the end of the tracheal cannula for two or six minutes, a rise in venous pressure from 15 to 20 mm. occurred, showing that the preparation was still in good condition. This seems to show that the venopressor rise after adrenalin is not due to any central mechanism, controlling the caliber of veins, but to a peripheral effect on sympathetic endings, such as takes place in the arterioles.

----- pulse rate per minute.

————— arterial pressure in mm. Hg.

..... superior cava pressure in mm. 2 per cent sodium citrate.

+++++ inferior cava pressure in mm. 2 per cent sodium citrate.

————— respiratory rate per minute.

Large dots indicate actual determinations.

Circles indicate that venous pressure cannula was tested and found free from clots.

Chart 4. Dog 17 A—Vagus nerves cooled.

Chart 5. Decerebrate cat 3—Adrenalin chloride injections, vagi cut between II and III.

Chart 6. Decerebrate cat 6—Adrenalin chloride injections, artificial respiration.

CHART NO. 7

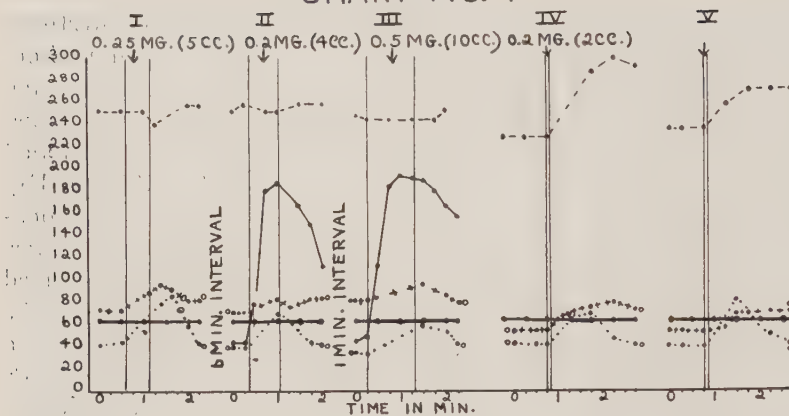


CHART NO. 8

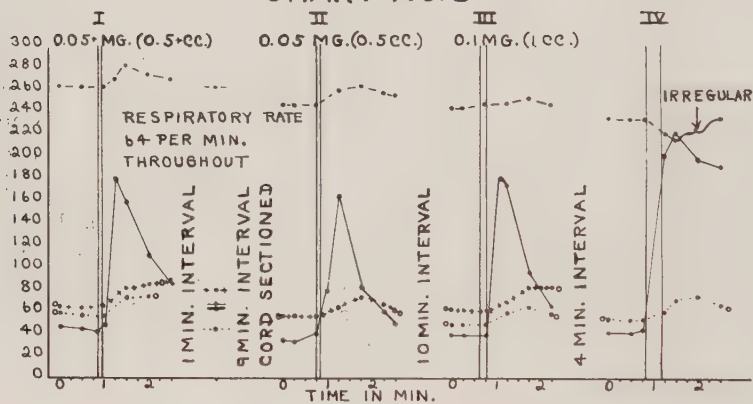
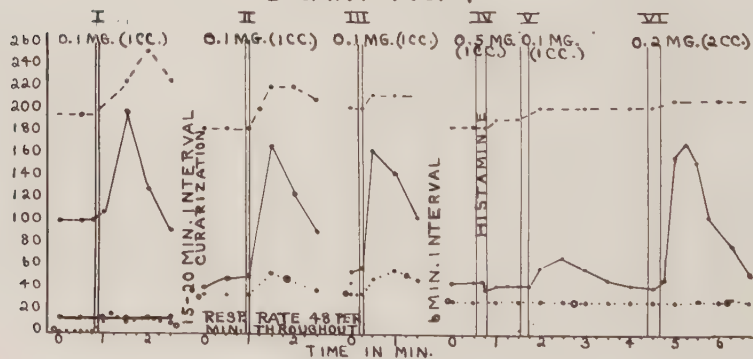


CHART NO. 9



Some experiments which were being carried out in this laboratory suggested that histamine might have an effect on the venopressor mechanism. Chart 9 (I, II, III) shows typical arterial and venous responses to adrenalin in a curarized, decerebrate cat. One-half milligram (1 cc.) of histamine (chart 9, IV) caused a fall in arterial pressure; in some experiments the venous pressure also fell. A more marked reaction was shown in another experiment, where twice the dose was given. According to Dale and Laidlaw (19), had the cat been under an anesthetic, these doses of histamine, from which the unanesthetized cat recovers, would have produced fatal circulatory collapse. When histamine was followed by adrenalin in the same and larger doses than given previously in the experiment, there was no venous pressure response (chart 9, V and VI). The arterial pressure rose, but not nearly as high as before, with the same dose. A second injection, however, gave a typical arterial pressure rise, but still no change in venous pressure. The work of Dale and Richards (20) and Dale and Laidlaw (19) leads them to conclude that relaxation of the capillaries is the cause of the vasodilator effect of histamine. The fall in venous pressure after histamine and the subsequent failure of the nervous mechanism to respond to adrenalin, indicates that histamine has a relaxing effect on venous tone, also, and acts in some way to depress the activity of the venopressor mechanism.

Summary. The various possible factors operating to produce the rise in venous blood pressure which occurs in dogs and cats after intravenous injection of adrenalin are discussed. The two factors chiefly responsible are the decreased heart rate bringing about decreased unit output of the heart, and a vasoconstrictor mechanism in the veins. The

----- pulse rate per minute.

————— arterial pressure in mm. Hg.

..... superior cava pressure in mm. 2 per cent sodium citrate.

+++++ inferior cava pressure in mm. 2 per cent sodium citrate.

————— respiratory rate per minute.

Large dots indicate actual determinations.

Circles indicate that venous pressure cannula was tested and found free from clots.

Chart 7. Adrenalin chloride injections: I, II and III, decerebrate cat 8—Vagi intact; cat curarized; artificial respiration; IV and V, decerebrate cat 9—Vagi cut; cat curarized; artificial respiration.

Chart 8. Decerebrate cat 15—Adrenalin chloride injections, before and after section of cord; vagi cut; cat curarized; artificial respiration.

Chart 9. Decerebrate cat 17—Adrenalin chloride injections, before and after histamine; vagi cut; cat curarized and artificial respiration begun between I and II.

effect of the first factor is accentuated by the fact that the arterial pressure is greatly raised by adrenalin in the doses here used. The first factor has been recognized before. Reasons are given why the second factor was previously overlooked. In dogs with good vagal tone and under an anesthetic, the rise in venous pressure is almost entirely due to the first factor. In cats whose vagal tone is not nearly as strong, the second factor predominates. This nervous mechanism is shown to be acted on peripherally by adrenalin, and to be depressed by ether, curare and histamine, especially the last.

I may take the opportunity here to thank Dr. W. H. Howell and Dr. D. R. Hooker of this University, and Dr. J. L. King of Goucher College, for kindly encouragement and aid in the preparation of this paper.

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